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Editorial

Should adjuvant chemotherapy be formally studied among patients found to have pelvic lymph node metastases following radical hysterectomy with lymphadenectomy for early-stage cervical cancer?

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The management of cervical cancer continues to evolve. Treatment guidelines are periodically reissued by the Japan Society of Gynecologic Oncology (JSGO), the European Society of Medical Oncology (ESMO), and the National Comprehensive Cancer Network (NCCN) and made available for oncologists practicing in Japan, the European Union, and the United States, respectively.

For example, the NCCN guidelines have recommended primary chemoradiation for the treatment of the International Federation of Gynecology and Obstetrics (FIGO) stage IB2 or greater in their guidelines since 2016 [1]. ESMO guidelines for the management of cervical cancer for FIGO stage IB2 or greater support primary surgical management with radical hysterectomy and pelvic lymph node versus primary chemoradiation [2]. Coincidingly the JSGO has recommended radical hysterectomy followed by risk stratification for adjuvant therapy versus primary chemoradiation as the treatment for FIGO stage IB–II cervical cancer in 2017 guidelines [3]. In Japan surgical treatment was chosen at a higher rate as the primary treatment for stages IB1 (90%), IB2 (79%), IIA1 (66%), IIA2 (59%), and IIB (44%) in a survey report of clinicians in 2014 [4].

While the JSGO, NCCN, and ESMO approach their guidelines using an evidence-based approach derived often from randomized clinical trials, FIGO updates the staging classification of gynecologic cancers through consensus in an effort to facilitate comparison of outcomes from different centers. Although no provision of treatment algorithms reside in the FIGO mandate, there are significant clinical implications that track with updated staging nomenclature. Importantly, in 2018 a major change was made in the FIGO staging of cervical cancer in that lymph node involvement (via histologic or radiologic assessment) is now designated as stage IIIC. This ramification was in response to the importance of lymph node metastasis as a major prognostic factor associated with decreased survival among women with early-stage and locally advanced disease [1].

In this issue of *Journal of Gynecologic Oncology*, Ikeda et al. [5] posed a similar question. The objective of the study was to evaluate the influence of the introduction of the JSGO published guidelines (2007) for the treatment of cervical cancer on clinical trends and outcomes for patients with early-stage cervical cancer who underwent surgery. This retrospective observational study utilized the JSOG cancer registry program database to evaluate postsurgical treatment and outcomes among 9,756 patients that underwent radical hysterectomy as primary treatment for cervical cancer from 2004 to 2009. Postsurgical management selections and outcomes were compared before the publication of the 2007 guidelines to after the publication of the guidelines. Results from the study showed that there was no significant difference in overall survival or in clinical practice trends after the introduction of the JSGO 2007 guidelines for the management of cervical cancer [5]. This study also specifically evaluated the influence of the guidelines on management and outcomes of early cervical cancer (pT1b1, pT1b2, pT2b) with positive lymph nodes.

Ikeda et al. [5] also suggest that differences in surgical technique among gynecologic oncologists may also play a role in postsurgical adjuvant therapy selection. Modifications have been made to the original technique of the radical hysterectomy over time. In Japan the Okabayashi method of radical hysterectomy technique is used and is considered more radical than other modifications; it is therefore believed to acquire greater rates of control of local pelvic disease. Additionally, in Japan it is common practice for a thorough pelvic lymph node dissection be completed. With the thought process that a more radical surgical technique has been performed, gynecologic oncologists may feel that systemic control with chemotherapy is more relevant than therapy that targets local disease control. In reality studies have found that though aggressive surgery followed by chemotherapy might decrease the rate of distant recurrence, patients have similar local recurrence rates [6]. A retrospective study by Hosaka et al. [7] found that radical surgical technique followed by chemoradiation may lead to higher morbidity than postsurgical chemotherapy alone.

The 2007 JSGO guidelines recommended that patients with pelvic lymph node metastasis receive postsurgical adjuvant therapy with either whole-pelvic irradiation or chemoradiation, and that the usefulness of adjuvant chemotherapy alone was unknown. Despite these recommendations, the study found that chemotherapy tended to be increasingly selected as postsurgical treatment in patients with early cervical cancer (pT1b1, pT1b2, pT2b) with positive lymph nodes, though this trend was not statistically significant [5]. As previously mentioned, positive lymph nodes are an important prognostic factor in cervical cancer, with a recurrence rate of greater than 40% compared to patients without lymph node metastasis. Lymph node involvement has also been shown to have a higher rate of distant failure [8-10]. Considering these findings, systemic chemotherapy has been proposed as postsurgical adjuvant therapy to control both local recurrence and prevent distant metastatic disease. Ikeda et al. [5] suggested that perhaps gynecologic oncologists considered positive pelvic lymph nodes as systemic disease that would not be sufficiently treated with local treatment with chemoradiation as was recommended by the guidelines. The benefit of chemotherapy as postsurgical treatment has not yet been clearly demonstrated [11]. Although the ongoing phase 3 randomized trial, GOG-0724 (NCT00980954), is studying the efficacy and tolerability of adjuvant chemotherapy in women with high-risk early stage disease who have been treated by radical hysterectomy with lymphadenectomy and postoperative chemoradiation, adjuvant chemotherapy alone has not yet been formally studied in this population. The observation by Ikeda et al. [5] that many oncologists have adopted postoperative adjuvant chemotherapy when nodal disease is detected indicates a gap in our knowledge concerning the natural

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history of the disease. The presence of pelvic nodal metastases may represent a harbinger of systemic disease. If this is the case, then perhaps it is finally time to study postoperative adjuvant chemotherapy alone among women with node-positive disease.

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